Original Research Paper

Study of Serum Malondialdehyde and Uric Acid in Pregnancy Induced Hypertension & Its Medico-Legal Significance

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Abstract

Pregnancy induced hypertension (PIH) remains the major cause of both maternal and foetal morbidity and mortality. While dealing with PIH women, the obstetricians have to be very careful to diagnose and properly manage the patients to prevent further progression of PIH disorders and complications so that charges of medical negligence against them may be avoided. The aim of the present study was to determine the association of serum malondialdehyde (MDA) and serum uric acid level with severity of PIH, and to correlate their medico-legal significance in avoiding the medical negligence charges. Study subjects included 70 PIH and 70 normotensive pregnant women of age group 18 - 40 years with gestational age >20 weeks. Highly significant increase ($p<0.001$) in systolic and diastolic blood pressure was recorded in PIH subjects. Serum MDA and uric acid level was also significantly elevated ($p<0.001$) in PIH subjects compared to the control subjects. Serum MDA and uric acid may be included as additional parameters for screening and progression of PIH. This may be helpful in effectively managing the PIH patients at an early stage thereby further avoiding medical negligence charges.

Key Words: Pregnancy induced hypertension, MDA, Uric acid, Medical Negligence

Introduction:

Litigations in Obstetrics are far more common than in any other sub-specialty of Medicine. Obstetricians deal with two lives at a time the mother who can be seen clinically, and her developing fetus whose wellbeing can only be predicted. One of the areas of common obstetrics suits is errors or omissions in antenatal clinical screening and diagnosis.

Most important one is the prediction and diagnosis of pregnancy induced hypertension (PIH). [1]PIH includes a group of hypertensive disorders developed due the gravid state after 20 weeks of pregnancy.

It includes gestational hypertension with blood pressure ≥140/90 mmHg without proteinuria; pre-eclampsia, which is gestational hypertension with proteinuria.

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Eclampsia, defined as pre-eclampsia with convulsions. Hypertensive disorders complicate 5 to 10% of all pregnancies, and together they form one member of the deadly triad, along with hemorrhage and infection, that contribute greatly to maternal morbidity and mortality rates. [2]

PIH is the most important cause of maternal and neonatal morbidity and mortality. Women with pre-eclampsia/eclampsia are at higher risk of obstetric complications like abruptio placentae and intra-uterine growth restriction as compared to normotensive women. The patho-physiology of PIH is still unclear, but an imbalance between reactive oxygen species (ROS) and antioxidants, also called oxidative stress has been attributed to be an important contributing factor. [3]

In healthy pregnancy, oxidation by free radicals and neutralization by antioxidants remains in balance. When the reactive oxygen species (ROS) are in abundance, oxidative stress occurs which is thought to be the causative factor in PIH.

Malondialdehyde (MDA) is the end product of lipid peroxidation and reflects the oxidative status of the biological system. MDA causes damage to LDL molecules. The altered LDL also called oxidized LDL is taken up by macrophages via scavenger receptors and forms foam cells which later results in

atherogenesis.[4] Hyperuricemia is believed to result from the decreased renal excretion that occurs as a consequence of the pre-eclampsia but this result is probably also due to increased production secondary to tissue ischemia and oxidative stress. Soluble uric acid impairs nitric oxide generation in endothelial cells. Hyperuricemia induces endothelial dysfunction and may induce hypertension and vascular disease in PIH. [5]

The association of serum MDA and uric acid with PIH is highly suggested to reflect some new diagnostic tools. Estimation of these parameters in pregnancy may be helpful in predicting the development of PIH and its progress can be monitored and managed effectively thereby preventing and/or reducing maternal and fetal complications.

The present study has been designed to determine the association of serum malondialdehyde (MDA) and serum uric acid level with the severity of PIH, and to correlate their medico-legal significance in avoiding the medical negligence charges.

Material & Methods:

This prospective one year (Jan. 2012 - Dec. 2012) case-control study was conducted in the department of Biochemistry in collaboration with the department of Obstetrics & Gynaecology, Rohilkhand Medical College & Hospital, Bareilly, U.P., India. Ethical clearance from Institutional Ethical Committee has been obtained and informed written consent from patients has been taken.

The present study included 140 pregnant women of age group 18 to 40 years with gestational age of >20 weeks. Seventy pregnant women with diagnosis of PIH and 70 healthy normotensive pregnant women undergoing antenatal care in OPD or admitted in the Obstetrics and Gynaecology ward at RMCH, Bareilly were randomly selected and constituted sample size.

The study subjects were divided into four groups as under:

- **Group I:** Women with gestational hypertension (GH), defined by systolic BP ≥140 or diastolic BP ≥90 mm Hg for first time during pregnancy (after 20 weeks of gestation) without proteinuria (n = 25).
- **Group II:** Women with pre-eclamptic toxemia (PE) with BP ≥140/90 mm Hg after 20 weeks' gestation with proteinuria ≥300 mg/24 hours or ≥1+ dipstick (n = 25).
- **Group III:** Toxemic women with eclampsia (E), defined by women presenting with convulsions/coma along with features of pre-eclampsia (n = 20).
- **Group IV:** Healthy normotensive pregnant women (N) (n = 70).

The enrolled subjects with the history of use of antioxidant supplementation, gestational diabetes, diabetes mellitus, chronic hypertension, coronary heart disease, impaired renal function, liver disorder, severe anaemia, gout, smoking, tobacco addiction & alcoholism were excluded from the study.

The blood pressure was recorded thrice at 5 minutes intervals and mean of three readings was noted following standard procedures. Women once found hypertensive, were screened for presence of protein in urine by using dipstick method.

4 ml of venous blood was taken aseptically in a serum separator evacuated blood tube (vacutainer) without anticoagulant. Samples were allowed to clot at 37 C° for 30 minutes. After clotting of the blood, each blood sample was centrifuged for 15 minutes at 2000 rotations per minute (rpm) to get a clear and cell free serum. The investigations were performed in laboratory of Biochemistry department, RMCH.

Biochemical Analysis included:

- Serum MDA by Thiobarbituric acid (TBA) method; and
- Serum uric acid (SUA) by enzymatic method.

Analysis was done by using semi auto analyzer ERBA and spectrophotometer in the department of Biochemistry.

Statistical analysis of variables was done by using independent student's t-test between PIH and control while ANOVA (analysis of variance) was applied within different study groups. Coefficient of correlation 'r' was determined between different variables by using Pearson product moment correlation. A p-value <0.05 was considered to be statistically significant.

Observations & Results:

The systolic blood pressure among PIH subjects was higher (156.31 ± 17.66) when compared with the control subjects (116.17 ± 8.57) and was statistically highly significant (p<0.001). Similarly, diastolic blood pressure was also significantly higher (p <0.001) in PIH subjects (107.74 ± 11.04) when compared with control subjects (74.66 ± 7.04). (Table 1)

In this study When the systolic blood pressure of the control group was compared with different PIH sub-groups, the difference was found to be highly significant (p <0.001). Systolic

BP of PIH group II was higher (153.52 ± 12.18) than group I (145.36 ± 7.80) though not statistically significant (p>0.05).

But systolic blood pressure in group III was significantly higher (173.5 ± 19.72) (p <0.001) when compared with the group I and group II. (Table 1)

Diastolic blood pressure in the control group was significantly lower (p <0.001) compared to the different PIH sub-groups. Diastolic BP (mm Hg) of group II was slightly higher (104.24 ± 8.72) than group I (102.64 ± 6.47) but it was not statistically significant (p>0.05). Further diastolic blood pressure in group III was significantly (p<0.001) higher (118.5 ± 11.01) when compared with the group I and group II. (Table 1)

In present study estimation of Serum MDA level and serum uric acid levels were determined in normotensive pregnant women (control subjects) and in PIH subjects and the data were compared.

Serum MDA level (mmols/L) in PIH subjects was higher (1.071 ± 0.26) as compared to the control subjects (0.42 ± 0.11) and this difference was highly significant (p<0.001). A similar significant difference (p<0.001) was noted for serum uric acid level between the PIH subjects (6.65 ± 1.36) and the control subjects (4.72 ± 0.85). (Table 2)

The comparison of serum MDA and uric acid levels within control and different PIH sub-groups were found significantly higher (p< 0.001) in PIH I, II and III sub-groups when compared with Group IV (normotensive pregnant women). Similarly MDA level in PIH group III was also found significantly higher (p<0.001) when compared with the other two PIH groups. Uric acid level was also found significantly higher in group III when compared with group I (p <0.01) and group II (p<0.05).

Coefficient of Correlation:

Variables that tend to correlate are likely to be altered during the disease process. Correlation was considered significant where p-values of 'r' was <0.05. A strong positive and statistically significant correlation was observed between systolic BP and MDA (r = 0.567 and p-value of 'r' 0.000. (Fig. 1)

There was no statistical correlation between systolic BP and uric acid (r = 0.214 and p-value of 'r' 0.075). (Table 3) A moderate positive and statistically significant correlation was found between diastolic BP and MDA (r = 0.443 and p-value of 'r' 0.000 (Fig. 2), & uric acid (r = 0.367 and p-value of 'r' 0.002. (Fig. 3)

A weak correlation was established between MDA and uric acid (r = 0.291 and p-value of 'r' 0.015). (Table 3)

Discussion:

Medical negligence has acquired a great significance during last two decades after the inclusion of medical services under the purview of Consumer Protection Act 1986.The number of cases of medical litigation is increasing which are becoming a curse especially in the field of surgery, anaesthesia, and obstetrics and gynaecology. In a retrospective study conducted by Janani et al [6] maximum numbers of medical negligence cases was related to surgical practice among which Obstetrics & Gynaecology ranked the highest (38.18%).

Pregnancy induced hypertension (PIH) continues to be a major health care related problem in pregnant women despite advancements in the field of medical sciences.

The spectrum of clinical presentation in PIH patients varies from mild, presenting only with small increase in blood pressure with/without protein in the urine, to severe maternal and fetal complications.

The major sign of PIH is hypertension, suggesting that it is due to vasospastic events in the placenta, kidney, uterus and brain. In our study, the mean systolic and diastolic blood pressure in PIH subjects were significantly higher (p <0.001) than those of control subjects, this observation was in agreement with other studies. [7-9]

This study indicates that the severity of PIH is associated with increase in blood pressure, both systolic and diastolic (Table 1) and this finding is consistent with the established fact. Hypertension develops through increased chemokine and cytokine expression, induction of the renin-angiotensin system and increased vascular C-reactive protein (CRP) expression in mother. [10] As the severity of the PIH increases, there is increase in the severity of the patho-physiological phenomenon leading to the accentuation of blood pressure.

This elevated blood pressure recovers within one month postpartum suggesting that the after expulsion of placenta which is said to be the reason for PIH, the altered physiology returns to the normal.

In our study the lipid peroxidation marker malondialdehyde (MDA), among the PIH subjects was significantly increased as compared to the normotensive pregnant women. Similar observations were noted by others. [7, 8, 11] Serum MDA was found significantly higher

(p <0.001) in all PIH sub-groups when compared with control group in the present study.

Similarly MDA level in eclamptic women was also found significantly higher (p <0.001) when compared with other two groups. Other studies conducted by Hubel et al [12] and Freud et al [13]have also shown that lipid peroxides like MDA were significantly elevated in mild and severe PIH. MDA level has also been noted to be increased during the progression of normal pregnancy as observed by Upaydhyaya [14] and Patil et al [15] but these levels are lower than in PIH subjects**.**

The increased MDA level in PIH is known to be due to increased generation of reactive oxygen species and reduction in anti-oxidants activity. Reactive oxygen species thus produced can cause enhanced lipid peroxidation in PIH which play a significant role in patho-physiology of PIH. [11]

A similar significant difference (p <0.001) as that of MDA, was noted for serum uric acid level between the PIH subjects and the control subjects. Kashinakunti et al [8] & Latha and Ganesan [9] also noted significant elevation of uric acid (p <0.001) in study group in comparison to controls in conformity with our observations. Hickman et al [16] also observed that women who developed hypertension had significantly higher uric acid levels than women who remained normotensive throughout the pregnancy.

In present study serum uric acid level was found significantly higher (p <0.001) in PIH patient groups when compared with normotensive pregnant women. Uric acid level was also found significantly higher in eclamptic women when compared with gestational hypertension (GH) (p <0.01) and pre-eclampsia (PE) (p <0.05) subjects. Level of serum uric acid in mild PIH was significantly higher than normo-tensive women noted by Mustaphi et al. [17]

In severe PIH, the mean serum uric acid levels were significantly more than control group and mild PIH group women. Punthumapol & Kittichotpanich [5] have observed thatthe mean serum uric acid in severe pre-eclamptic women was more than normal pregnant women and mild pre-eclamptic women. But there was no significant difference between normal pregnant women and mild pre-eclamptic women.

Plasma uric acid concentration is typically elevated in PIH. It likely results from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption, and decreased secretion.

Another possibility is from increased placental urate production compensatory to increased oxidative stress. Recently increased oxidative stress and formation of reactive oxygen species (ROS) have been proposed as another contributing source of Hyperuricemia noted in PIH apart from renal dysfunction. [18]

Though often considered an antioxidant, biochemical and in-vitro data indicates that non-crystalline, soluble uric acid can react to form radicals, increase lipid peroxidation and induce various pro-oxidant effects in vascular cells. [10]

From in-vitro and in-vivo studies, uric acid may contribute to endothelial dysfunction through inducing anti-proliferative effects on endothelium and impairing nitric oxide production in vascular smooth muscle cells (VSMCs). [10] Elevated uric acid levels in PIH women may not simply be a marker of disease severity but possibly contribute directly to the pathogenesis of the PIH. [19]

Correlation of MDA and uric acid was studied with systolic and diastolic blood pressure and a significant positive correlation between MDA and systolic (r = 0.567, p <0.001) and diastolic (r = 0.443, p <0.001) blood pressure was observed. A significant positive association was also observed by Bayhan et al [20] between serum MDA level and systolic blood pressure in women with severe pre-eclampsia (r = 0.375, p = 0.049) supporting our findings**.**

In contrast to our findings, Sahu et al [7] noted a negative correlation of diastolic BP with MDA (p <0.05) in PIH women. Bayhan et al [21] observed no correlations between serum levels of lipid peroxide and systolic-diastolic blood pressure of pregnant women with pre-eclampsia and eclampsia in variance to our observations.

The strong significant relationship between MDA and systolic-diastolic blood pressure in PIH suggests an increased susceptibility to vascular disease and development of PIH which is associated with oxidative stress in these patients. This therefore, suggests that PIH is associated with oxidative stress reflected by elevated MDA level as a result of lipid peroxidation during pregnancy.

On the other hand, uric acid has been significantly correlated only with diastolic blood pressure. For diagnosing PIH, diastolic blood pressure is more specifically taken into consideration as compared to the systolic blood pressure as it may also increase due to other non-specific factors.

Latha and Ganesan [9] correlated blood pressure with uric acid in PIH groups. They showed significant positive correlation of uric acid with both systolic and diastolic blood pressure which is in contrast to our observations except that with diastolic blood pressure.

Mustaphi et al [17] and Varma [22] observed that when the level of diastolic blood pressure increased, the level of serum uric acid was also increased and there has been a positive correlation between diastolic blood pressure and serum uric acid levels.

In contrast, Hickman et al [16] concluded that the serum uric acid level was an unreliable indicator of developing hypertension in the individual woman. Many authors believed that uric acid is one of the most consistent and earliest detectable changing parameter that occurs in PIH and have been cited as a better predictor of fetal risk than blood pressure. [19]

Conclusions:

The association of MDA and uric acid with severity of PIH is highly suggested to reflect some new diagnostic tools. In the present study, a positive correlation has been made out between serum MDA and uric acid with the severity of PIH and these may be useful markers and diagnostic tools for predicting the progression of PIH and thereby preventing and reducing maternal as well fetal complications by timely intervention, thus curtailing charges of negligence and litigations.

Though our study has provided a reasonable level of evidence that these two surrogate markers are important predictor of PIH yet further investigations are required to determine the comprehensive mechanism of this correlation.

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Table 3: Coefficient of Correlation

X-axis Vs. Y-axis		Coefficient of Correlation 'r'	p-value of 'r'
Systolic BP	MDA	0.567	<0.001
Systolic BP	Uric acid	0.214	>0.05
Diastolic BP	MDA	0.443	<0.001
Diastolic BP	Uric acid	0.367	<0.01
MDA	Uric acid	0.291	<0.05

Fig. 1: Correlation between Systolic Blood Pressure and MDA in PIH Subjects

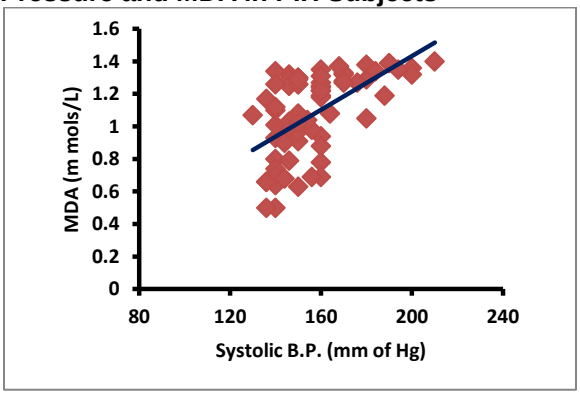

Fig. 2: Correlation between Diastolic Blood Pressure and MDA in PIH Subjects

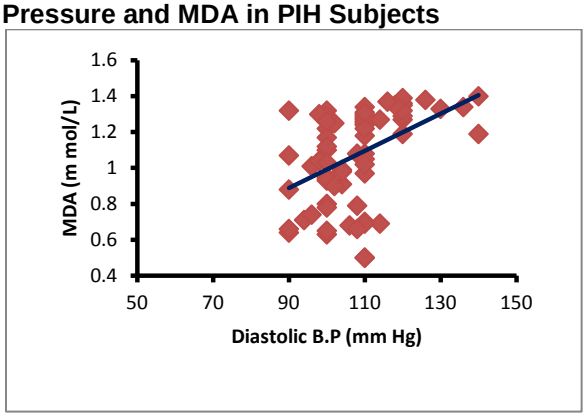

Fig. 3: Correlation between Diastolic Blood Pressure and Uric Acid in PIH Subjects

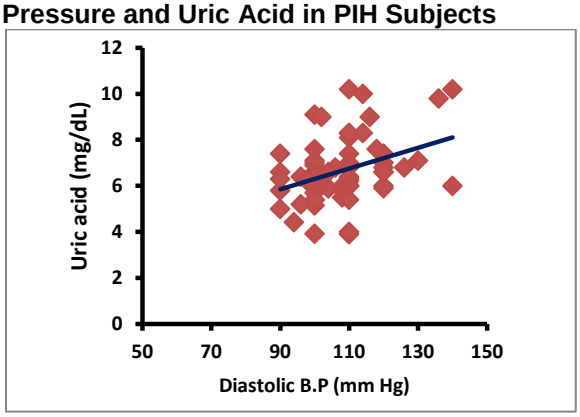

Table 1
Comparison of Blood Pressure between PIH and Control Subjects and within PIH sub-groups

Blood Pressure	PIH Group I (GH) (Mean ± S.D.) n = 25	PIH Group II (PE) (Mean ± S.D.) n = 25	PIH Group III (E) (Mean ± S.D.) n = 20	Total PIH Cases (Mean ± S.D.) n = 70	Group IV (Control) (Mean ± S.D.) n = 70
Systolic BP (mm Hg)	145.36 ± 7.80	153.52 ± 12.18	173.5 ± 19.72	156.31 ± 17.66	116.17 ± 8.57
Diastolic BP (mm Hg)	102.64 ± 6.47	104.24 ± 8.72	118.5 ± 11.01	107.74 ± 11.04	74.66 ± 7.04

Table 2
Comparison of MDA & Uric acid level between PIH with Control Subjects and within PIH sub-groups

Serum Levels	PIH Group I(GH) (Mean ± S.D.)	PIH Group II (PE) (Mean ± S.D.)	PIH Group III(E) (Mean ± S.D.)	Total PIH subjects (Mean ± S.D.)	Group IV (Control) (Mean ± S.D.)
MDA (mmols/L)	0.78 ± 0.15	1.17 ± 0.12	1.31 ± 0.06	1.071 ± 0.26	0.42 ± 0.11
S. Uric acid (mg/dl)	5.99 ± 1.01	6.81 ± 1.37	7.27 ± 1.41	6.65 ± 1.36	4.72 ± 0.85